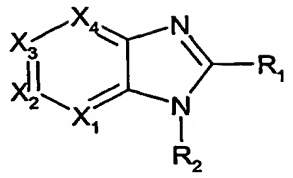
Claims

1. A compound of the general formula (I)



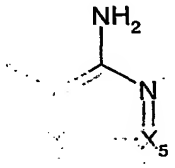
(I)

and physiologically acceptable salts and or N-oxides thereof wherein,

X_1 is N or CR_3; X_2 isN or CR_4; X_3 is N or CR_5; X_4 is N or CR_6.

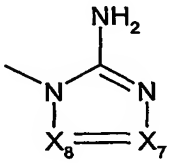
with the proviso that at least one but not more than two of X_1, X_2, X_3 and X_4 represents N.

R_1 is a 5-, or 6- membered heterocyclic group selected from group a, b, c or d



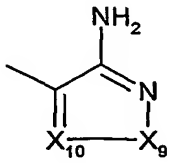
(a)

wherein X_5 is a group selected from N or CR_7 and X_6 is a group selected from O, S or NR_8;



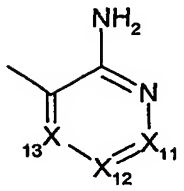
(b)

wherein X_7 and X_8 which may be the same or different is a group selected from N or CR_9;



(c)

wherein X_9 is a group selected from O, S or NR_8 and X_{10} is N or CR_{10};



(d)

wherein X_{11}, X_{12} and X_{13} may be the same or different and selected from a group N or CR_{11};

R_2 and R_8 independently represents hydrogen, hydroxy, aryl, heteroaryl, C_{3-7}cycloalkyl, heterocyclyl, a group YR_{12}, $N=R_{13}$, $CONR_{14}R_{15}$, $COCH_2NR_{19}R_{20}$,$NR_{14}COR_{16}$, $SO_2NR_{14}R_{15}$ or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, acylamino, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, $SO_2NR_{14}R_{15}$, $CONR_{14}R_{15}$, $NR_{14}COR_{16}$, $OalkNR_{19}R_{20}$, $SalkNR_{19}R_{20}$ or NR

R_3, [illegible]$_9$,R_{10} and R_{11} independently represent a group selected from hydrogen, halogen, hydroxy, $R_{19}O$, $R_{19}S(O)_n$, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, nitro, formyl, C_{1-4}alkanoyl, alkenyl (optionally substituted by optionally substituted phenyl, heterocyclyl, or heteoaryl), carboxy, optionally substituted phenyl, heteroaryl, cycloalkyl, cycloalkylalkyl, aryloxy, heteroaryloxy, heterocyclyl, $CONR_{14}R_{15}$, $NR_{14}COR_{16}$, $SO_2NR_{14}R_{15}$, $NR_{17}SO_2R_{18}$or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, acylamino, hydroxy, $CONR_{14}R_{16}$, $NR_{14}COR_{16}$, $SO_2NR_{14}R_{15}$, $NR_{17}SO_2R_{18}$, $OalkNR_{19}R_{20}$, or $SalkNR_{19}R_{20}$ group];

R_{19} and R_{20} independently represent a group selected from C_{1-6} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl;

Y represents O, NH,NR_{12} or $S(O)_n$;

R_{12} represents aryl, heteroaryl, cycloalkyl, heterocyclyl or C_{1-6}alkyl [optionally substituted

by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, acylamino, hydroxy, $CONR_{14}R_{15}$, $NR_{14}COR_{16}$, $SO_2NR_{14}R_{15}$, $NR_{17}SO_2R_{18}$ $OalkNR_{19}R_{20}$, or $SalkNR_{19}R_{20}$ group];

R_{13} represents an alkylidene group which may be substituted by an aryl, heteroaryl, heterocyclyl or cycloalkyl group or R_{13} represents a cycloalkylidene or heterocycloalkylidene group.

R_{14} and R_{15} independently represent hydrogen, aryl, heteroaryl, cycloalkyl or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, or acylamino group] or R_{14} and R_{15} together with the nitrogen atom to which they are attached form a 4-7 heterocyclic ring which may be saturated or unsaturated and optionally contains another heteroatom selected from O,N or $S(O)_n$;

R_{16} and R_{18} independently represent ,aryl, heteroaryl, heterocyclyl,cycloalkyl or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, or acylamino group] or the group $NR_{14}R_{15}$ wherein R_{14} and R_{15} have the meanings defined above;

R_{17} represents hydrogen, aryl, heteroaryl, heterocyclyl, cycloalkyl or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, or acylamino group];

Alk is a C_{2-4} straight or branched alkylene chain

n is zero, 1 or 2.

2. A compounds as claimed in claim wherein only one of X_1, X_2, X_3 or X_4 represents N.
3. A compound as claimed in claim2 wherein X_2 or X_3 represent N .
4. A compound as claimed in any of claims 1 to 3 wherein X_3 represents N
5. A compound as claimed in claim 1 wherein X_1 and X_3 each represents N .

6. A compound as claimed in any of claims 1 to 5 wherein R_1 is a group selected from (c) or (d).

7. A compound as claimed in any of claims 1 to 6 wherein R_1 is a group (c) in which X_9 is oxygen and X_{10} is nitrogen.

8. A compound as claimed in any of claims 1 to 7 wherein R_2 represents hydrogen, C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylmethyl, phenyl or phenyl substituted by(amino, dialkylamino, dialkylaminoalkylamino, alkyl , alkanoyl, alkoxy, halo,hydroxy, aminoalkyl, hydroxalkoxy, aminoalkoxy, alkylaminoalkoxy, N-aralkyl-Nalkylaminoalkoxy,aminocarbonylalkoxy,alkylaminocarbonylalkoxy, dialkylaminocarbonylalkoxy, ureidoalkoxy, alkylureido, dialkylamino-acetamido, alkylthioalkoxy, phenylthioalkoxy, alklsulphinylalkoxy, phenylsulphinylalkoxy, alkylsulphonylalkoxy, phenylsulphonylalkoxy, cyanoalkoxy, acylaminoethoxy, alkylsuphonylaminoalkoxy phenylsulphonylaminoalkoxy, alkoxycarbonylalkoxy, heterocyclylalkoxy, heterocyclyloxy, heterocyclyl), alkyl substituted by (hydroxy, amino, acylamino, $R_{19}NH$, $R_{19}R_{20}N$, a 4-7-membered heterocyclyl group, a 4-7 membered heterocyclyl group, a 5,6 fused bicyclic hetroaryl group, a 6,6 fused bicycliheterocyclic group, a 6,5 fused heterocyclic group or a 6,7 fused heterocyclic group.

9 A compound as claimed in any of claims 1 to 8 wherein R_2 represents hydrogen, methyl, ethyl, isopropyl, sec butyl, 2-ethylbutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropylmethyl, cyclohexylmethyl, phenyl , phenyl substituted by[amino 4 - dimethylamino, dimethylaminoethylamino, N-methyl,dimethylaminoethylamino, N,N-bis(2-dimethylaminoethyl)amino), ethyl,acetyl, methoxy 3-methylbutoxy, chlorine , bromine,hydroxy, aminomethyl, 2-hydroxyethoxy ,3-hydroxypropoxy, 2- aminoethoxy, 2-methylaminoethoxy, 2-dimethylaminoethoxy, 2 diethylaminoethoxy, 2 diethylamino-1-methylethoxy, 2-disopropylamino-1-methylethoxy, N N-benzyl N-methylaminoethoxy, aminocarbonylmethoxy, aminocarbonyl-2-methylethoxy, aminocarbonylethoxy, methylaminocarbonylmethoxy, dimethylaminocarboxymethoxy, ureidomethoxy, 3-

methylureido, dimethylaminoacetamido, methylthiomethoxy, phenylthiomethoxy, methylsulphinylmethoxy, phenylsulphinylmethoxy, methylsulphonylmethoxy, phenylsulphonylmethoxy, cyanomethoxy , 2-cyanoethoxy, t -butoxycarbonylaminoethoxy, isoxazolylaminoethoxy, isonicotinylaminoethoxy, methylsulphonylaminoethoxy, phenylsulphonylaminoethoxy, 2-methoxycarbonyl 1-methylethoxy, morpholinoethoxy, piperidinoethoxy, 1-pyrroldino-2-ylmethoxy, 1-methyl-piperidino-4-yloxy or3-pyrrolidinyl,] 2-hydroxy-1-methyl-ethyl, 3- aminopropyl, 4-aminobutyl, 5 aminopentyl , 4-butyloxycarbonylamino-butyl , 2-dimethylamino-1-methylethyl, 4-diethylamino-1-methyl- butyl , 3-dimethylaminopropyl, 4-methylpiperazin-1-ethyl, 2-piperazin-yl-ethyl, piperidine 4-yl methyl , piperidine 3-yl methyl, piperidin-4-yl , piperidin-3-yl, pyrrolidin-3-yl, 5-indazolyl or 6-indazolyl, . tetrahydroisoquinolin-5-yl, 2-methyl tetrahydroisoquinolin-7-yl, 2-methanesulphonyl-tetrahydroisoquinolin-7-yl, tetrahydroisoquinolin-7-yl, 3,4 dihydro-2H-isoquinolin-1-one-7-yl , 2,3-dihydro-1H-isoindol-5-yl, benzo{1,3]dioxol-5-yl or 2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl

10 A compound as claimed in any of claims 1 to 9 wherein R_3 represents hydrogen, halogen , hydroxy , carboxyl, phenyl or phenyl (substituted by one or two groups selected from alkoxy, hydroxy, hydroxymethyl, trifluoromethyl, trifluoromethoxy, amino, acetamido, aminoalkyl, alkyl, carboxyl carboxamido, N,N-dimethylcarboxamido, cyano, formyl, phenoxy, $CH_3S(O)n$ wherein n is zero,1 or2, CH_3SO_2NH,or halogen), or heterocyclyl, heteroaryl , 6,5-fused bicycloheterocyclyl , an optionally substituted phenyl substituted by the group $CH_2NR_{19}R_{20}$ wherein R_{19} is alkyl, phenyl or a heterocyclic group and R_{20} is hydrogen or methyl, or $NR_{19}R_{20}$ is a 4-7 heterocyclic group, alkyl substituted by (a 4-7 membered heterocyclyl group or a group $NR_{19}R_{20}$ (wherein R_{19} is hydroxylalkyl, optionally substituted benzyl, C $_{3-7}$ cycloalkyl, a heterocyclic group, a 4-7 membered heterocycylalkyl or C $_{3-7}$ cycloalkylalkyl, R_{20} is hydrogen, methyl or acetyl),

4-heterocyclyoxy,heterocyclylalkyloxy ,vinyl (optionally substituted by optionally substituted phenyl), $CONR_{14}R_{15}$

wherein R_{15} is hydrogen, R_{14} is benzyl, phenethyl, aminoalkyl , 4-7 membered heterocyclyl or4-7 membered heterocyclylalkyl, or R_{14} and R_{15} together with the nitrogen atom to which they are attached represent a 4-7 membered heterocyclyl group, a group $R_{19}S(O)n$(wherein n is zero, 1 or 2 and R_{19} is optionally substituted phenyl),or a group $R_{19}NH$ and R_{19} is optionally substitued phenyl or heteroaryl.

11 A compound as claimed in any of claims 1 to10 wherein R_3 represents hydrogen, bromine, hydroxy , carboxyl, phenyl or phenyl (substituted by one or two groups selected from methoxy , ethoxy, hydroxy, hydroxymethyl, trifluoromethyl, trifluoromethoxy, amino, acetamido, aminomethyl, aminoethyl, methyl , ethyl, carboxyl, carboxamido, N,N-dimethylcarboxamido, cyano, formyl,. phenoxy, $CH_3S(O)n$ wherein n is zero,1 or 2, CH_3SO_2NH,or fluorine), 5-methyl-1,2,4-oxadiazol-3-yl, 2-thienyl, 4-methylthienyl, 5-phenylthienyl, [illegible]nyl, or 3-thienyl, 2-furanyl, pyridyl such as 3-pyridyl or 4-pyridyl, 3,5-dimet[illegible]adolyl or 8-quinolinyl, benzothienyl, 5-benzo[1,3]dioxolyl, a phenyl or fluorophenyl substituted by the group $CH_2NR_{19}R_{20}$ (wherein $NR_{19}R_{20}$ represents ethylamino, dimethylamino, 4-morpholino, pyrrolidino, piperidino, piperidin-4-yl-amino or 1-t butoxycarbonyl-piperdin-4-yl-amino.), 3-hydroxypropylamino, 4-bromobenzylamino, 4-methoxybenzylamino, 4-piperidinylaminomethyl, N-4-piperidinyl-N-methylaminomethyl, 1-t butyoxycarbonyl-piperidinyl-aminomethyl

4-aminopiperidinomethyl,1,4-diazepan-1-ylmethyl, piperazinomethyl, 4-methylpiperazinomethyl, 4-acetylpiperizin-1-ylmethyl, 4- ethylpiperazinomethyl 4-morpholinomethyl, piperidinomethyl, 4-(methylamino)piperidinomethyl, 4-cyclopropylaminopiperidinomethyl, pyrrolidinomethyl, 3-dimethylaminopyrrolidinomethyl, 2-hydroxymethylpyrrolidinomethyl, 4-ethylpiperazino-methyl, 3-pyrrolidin-1-yl-propylaminomethyl, 4-(4-fluorophenyl) piperazinomethyl, 3-piperidinyl-1-yl-propylaminomethyl, 3-morpholin-4-yl-propylaminomethyl, 3-(4-methylpiperazin-yl

propylaminomethyl, 1-methyl piperidin-4-yl-aminomethyl, 4-pyrrolidinocarbonylmethyl-piperazinomethyl, 2-pyrrolidin-1-ylmethylpyrrolidinomethyl, 2-pyrrolidin-1-yl-ethylaminomethyl, 3-dimethylaminopyrrolidinomethyl, 1-methyl-piperidin-4-ylaminomethyl, 1-isopropyl-piperidin-4-ylaminomethyl, 3-dimethylaminopyrrolidinomethyl, 2-(morpholin-yl-methyl)-pyrrolidinomethyl, 3-piperidin-1-yl-propylaminomethyl, 3-morpholin-4-yl-propylaminomethyl, 3-(4-methylpiperazin-1-ylpropylaminomethyl, piperidin-1-ylmethylpyrrolidinomethyl, 3,5-dimethylpiperazinomethyl, pyrrolidin-1-ylpiperidinomethyl, pyrrolidino-3-ylaminomethyl, pyrrolidin-2-ylmethylaminomethyl, 4-aminomethylcyclohexymethylaminomethyl, 4-aminocyclohexylaminomethyl, 2-piperazin-1-ylethylamoinomethyl, 3-amino-pyrrolidinomethyl, pyrrolidino-2-ylmethylaminomethyl, piperidin-4-ylmethylaminomethyl ,4-aminomethylpiperdininomethyl, 4-(cyclopropylaminopiperidinomethyl,
3-(piperazino-1-yl) propylaminomethyl, 2-(morpholin-4ylmethyl)pyrrolidinomethyl
2-(piperidin-1-ylmethyl)pyrrolidinomethyl, 2-(piperazin-1-ylmethyl)pyrrolidinomethyl, piperidin-4-ylmethyl, N-piperidin-4-yl-acetamidomethyl,. piperidin-4-yloxy, or piperidin-4-ylmethyloxy,
4-methyloxystyryl ,$CONR_{14}R_{15}$
wherein R_{15} is hydrogen, R_{14} is benzyl, phenethyl, 3-aminopropyl, 4-aminobutyl, 6-aminohexyl ,3 or 4-piperidinyl 1-aminomethylcarbonyl-piperidin-4-yl, 3-pyrroldinyl, piperidin-2-ylmethyl or piperidin-4-ylmethyl, morpholin-2-ylmethyl or piperazinoethyl, or R_{14} and R_{15} together with the nitrogen atom to which they are attached represent piperazino, 1-methylpiperazino, 4-(2-aminoethyl)piperazino,4-(t- butoxycarbonylaminoethyl)piperazino, . 4-aminomethylcarbonylpiperazino, 4-aminoethylcarbonylpiperazino, 4-1-(aminoethylcarbonylpiperazino, 4-(1-methylaminoethylcarbonylpiperazino .4-pyrrolidin-2-yl-carbonylpiperazino, pyrrolidino, 3-aminopyrrolidino , 2-methoxycarbonylpyrrolidino, morpholino, 2 (pyrrolidin-1yl)methyl pyrrolidino , a group $R_{19}S(O)n$ wherein n is zero, and

R_{19} is phenyl optionally substituted by methoxy ,a group $R_{19}NH$ whereinR$_{19}$ is phenyl, 4-morpholinophenyl or 3-aminopyridyl.

12 A compound as claimed in any of claims 1 to 11 wherein R_4 is hydrogen, methyl, methoxy, methylthio, phenylamino or phenoxy optionally substituted by fluorine or acetamido.

13 A compound as claimed in any of claims 1 to 12 wherein R_5 is hydrogen, methyl, methoxy or phenoxy.

14 A compound as claimed in any of claims 1 to 13 wherein R_6 is hydrogen, chlorine , hydroxymethyl, methyl, methoxy, phenyl, 1- pyrrolidinyl or 1- pyrazolyl.

15 A pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt and or an N oxide thereof together with one or more pharmaceutically acceptable excipients and /or carriers .

16 A compound of formula (I) and/or physiologically acceptable salts [illegible] for use in therapy .

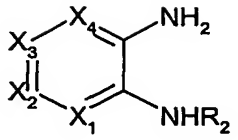
17 The use of a compound of formula (I) and/or a physiologically acceptable salt thereof in the manufacture of a medicament for inhibiting the effects of the kinase Msk-1 and or Rho-kinase 1 and or 2.

18 A method for inhibiting the effects of the kinase MSK-1 and or Rho-kinase 1 and or 2 comprising administering to a patient in need thereof an effective amount of a compound of formula (I) and/or a physiologically acceptable salt thereof.

19 A process for preparing a compound of formula (I) which comprises :-

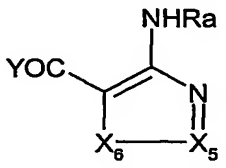
a) a process for preparing compounds of formula (I) wherein R_1 is a group (a), (c) and

(d) by reacting the diamine (II)

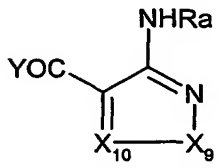


(II)

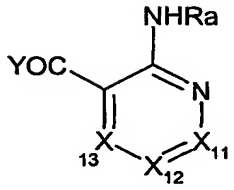
wherein R_2, X_1, X_2 , X_3 and X_4 have the meanings defined in (I) with the appropriate compound of formula (III), (IV) or (V)



(III)



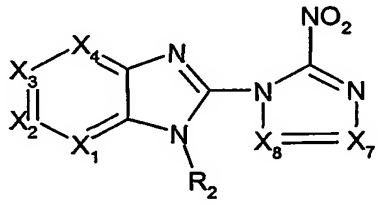
(IV)



(V)

wherein Y is hydrogen , halogen e.g. Cl, Br or I, hydroxy or C_{1-4}alkoxy, Ra is hydrogen or a nitrogen protecting group such as an alkoxycarbonyl or benzyloxycarbonyl group and each of X_5, X_6, X_9, X_{10}, X_{11}, X_{12} and X_{13} have the meanings defined in formula (I) or is a group available thereto, followed when required by removal of the nitrogen protecting group Ra using conventional methods.

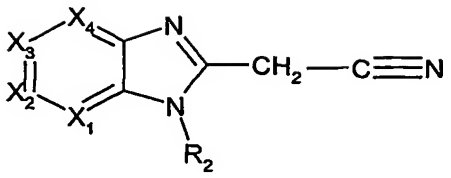
b) a process for preparing compounds of formula (I) wherein R_1 is the group (b) reducing of the corresponding nitro derivative (VI)



(VI)

wherein R_2, R_3, R_3, X_1, X_2, X_3, X_4, X_7 and X_8 have the meanings defined in formula (I).

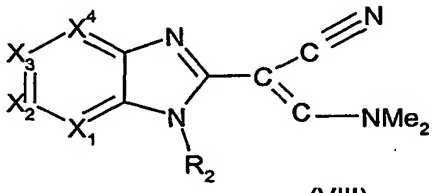
c) a process for the preparation compounds of formula (I) wherein R_1 is the group (c) and X_9 is oxygen and X_{10} is nitrogen may be prepared by reacting the nitrile (VII)



(VII)

wherein R_2, X_1, X_2, X_3 and X_4 have the meanings defined in formula (I) with hydrochloric acid and sodium nitrite in a solvent and treatment of the product thus formed with a and hydroxylamine.

d) a process for preparing a compounds of formula (I) wherein R_1 represent the group (c) and wherein X_9 is NH and X_{10} is CH may be prepared by reacting compound (VIII)



(VIII)

wherein R_2, X_1, [illegible] have the meanings defined in formula (I) with hydrazine.

and if necessary or desired:-

i remoal of any protecting groups

ii converting one compound of the invention into another

iii isolating the product of the reaction as a salt and or a solvate thereof